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TITLE: Do Structural Missense Variants in the ATM Gene Found in Women with Breast Cancer Cause Breast Cancer in "Knock-in" Mouse Strains?

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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U.S. Army Medical Research and Materiel Command
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14. ABSTRACT
The central hypothesis is that knock-in mice lines are made for two human cohort-specific missense mutations will develop breast cancer with dominant inheritance in a subset of animals. It also is hypothesized that other cancers will be more frequent as well. If correct, it follows that the ATM gene is the first known example of a "sup-oncogene", i.e., a tumor suppressor gene for lymphoma /leukemia and an oncogene for breast cancer. More generally, it is hypothesized that an increased risk for breast cancer due to ATM mutations most commonly derives from cohort-specific missense mutation, that do not cause A-T in a homozygous state and occasionally from a subset of A-T carriers that have non-truncating mutations. Two in human cohort-specific missense variants from our previous case-control analysis will be generated in mice using mouse knock-in technology. The rate and time course of cancer incidence will be determined in these mice in comparison to wild type littermates and an A-T- causing non-truncating structural variant. Since the mouse Atm gene is extremely close to the human gene in structure and function, mouse models with only a single alteration in the gene can be used to assess the effects of this alteration on tumor formation, especially mammary tumors, in mice. If a variety of uncommon missense variants are shown to predispose to breast cancer, there are important diagnostic, preventive, and therapeutic I implications for women at risk for breast cancer.

15. SUBJECT TERMS
ATM mutation, breast cancer, prognosis

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Table of Contents

Proposal Title: Do Structural Missense Variants In The ATM Gene Found In Women With Breast Cancer Cause Breast Cancer in "Knock-in" Mouse Strains?

Introduction

The recessive neurological disease ataxia telangiectasia (A-T), which has pleiotrophic effects including an increased susceptibility to cancer, is known to be caused by homozygous or compound heterozygous mutations in the ATM gene. In a number of epidemiological studies of A-T families, heterozygous carriers have been shown to be at increased risk of breast cancer. However, a number of early studies of breast cancer patients in non-A-T families did not detect a significant number of ATM truncating mutations. Our laboratory has conducted a case control analysis of 90 women with state 1 or 2 breast cancer who were referred for adjuvant radiation therapy. We determined that uncommon *missense* mutations, predominately at evolutionarily conserved amino acids, are associated with a 3.2 fold relative risk of developing breast cancer in individuals with such mutations relative to the breast cancer risk in normal population. From these data it is estimated that 13% of breast cancer cases in the population are due to these types of ATM missense mutations. Most disturbing is preliminary evidence that such individuals may harbor a much greater likelihood of recurrence relative to those individuals without such mutations.

These result can perhaps be integrated by testing the following hypothesis: in heterozygotes, truncating mutations causing total disruption of ATM function do not predispose to breast cancer, whereas missense mutations that alter ATM function do predispose to breast cancer. Therefore, increased risk of breast cancer in ataxia telangiectasia heterozygotes may be due to the missense mutations in approximately 30% of patients. Preliminary data suggest that women with ATM-mediated breast cancer have poor prognosis.

There is an overriding need to unequivocally determine the magnitude of breast cancer risk associate with ATM missense mutations. A second, more robust, approach would involve the murine model of the Atm locus, in which targeted mutations are introduced into the Atm gene to determine whether certain *missense* variants (rather than truncating mutations causing total disruption of ATM function) predispose to breast cancer in mice. The importance of the mouse model cannot be over-emphasized, since mouse genes are similar to their human counterparts, serve the same purpose, and mutations often mimic the corresponding human phenotype. The entire coding sequence of the mouse homolog of the human ATM gene has been cloned, cytogenetically mapped, molecularly characterized and was found to be remarkably similar to the human gene. Furthermore, mouse studies of the Atm locus indicate that absence of Atm activity in heterozygotes produces an ataxia-telangiectasia phenotype, whereas heterozygotes containing a small in-frame deletion for a mutant, but expressed, form of Atm exhibit a greater susceptibility to breast cancer.

We propose an innovative and as yet untried series of experiments to construct and analyze selected murine missense and truncating Atm mutations which, in combination with our ongoing human ATM mutation studies, has the potential to clearly and cleanly demonstrate a major role of certain ATM structural variants in the predisposition to breast cancer.

Body

Task 1. To construct two vectors containing specific missense variants found in the ATM gene of breast cancer patients in a mouse Atm clone.

a. This work is being initiated before the start of this grant by inGenious Targeting Laboratory (iTL).
b. A BAC library will be screened for mouse Atm clones.
c. Two subclones will be isolated for the regions of interest.
d. Two knock-in targeting vectors containing the variants of interest will be constructed.

Task 2. To produce two mouse knock-in Atm lines. Production of the second line will be staggered by about two months (Months 1-8).

a. Vector DNA will be transfected into 129/S6 embryonic stem (ES) cell lines and about 300 clones will be produced (Months 1-4).
b. Clones will be screened by Southern blotting to determine those that carry the targeted mutation (Months 3-5).
c. Clones positive for the targeted mutation will be expanded and injected into C57BL/6 blastocysts to produce chimeras for germline transmission. Tail biopsies of mice potentially heterozygous for the targeted mutation will be genotyped (Months 4-8).

Constructing the vectors has produced unanticipated challenges.

After a false start with a commercial entity, we are generating the two vectors in house. Although we are a technically oriented laboratory (see CV), we have not had previous experience in vector construction. I anticipate that Task 1 will be complete in two months and Task 2 will be complete within six months. We are in the queue with the transgenic mouse core facility to inject oocytes when the vectors are complete.

Meanwhile in relevant work <u>not</u> funded by this grant, we have generated more evidence in support of the central hypothesis underlying the transgenic knock-in mice being created with these funds.

The current analysis expands upon case control epidemiological analyses of the ATM gene in women with overwhelming Stage I or Stage II breast cancer vs. ethnically similar controls (Singh et al.) *Submitted*

We find that women with cohort-specific ATM mutations have substantially poorer prognosis than those who do not have ATM cohort specific structural variants.

The following is an abstract from our submitted publication.

Ataxia-Telangiectasia A-T is an autosomal recessive disorder characterized by progressive cerebellar degeneration, telangiectasias, radiosensitivity, immunodeficiency, and a predisposition to cancer development. Epidemiologic studies of families of A-T patients have demonstrated an increased risk of breast cancer in females. Furthermore, in a recently reported series, we observed a significant elevation of cohort-specific missense ATM mutations insufficient to cause A-T in 90 breast cancer patients as compared to ethnically matched controls.

We retrospectively reviewed the records of breast cancer cases for correlation with clinical features including age at diagnosis, histology, tumor size, axillary nodal metastases, disease control, acute toxicity of radiation therapy, and long-term sequelae. Freedom from relapse (FFR) was determined by the method of Kaplan & Meier and analyzed by the generalized Wilkoxon test.

FFR was significantly shorter in patients with cohort-specific mutations in the ATM gene relative to those without cohort-specific mutations ($p = 0.0001$). With the exception of cohort-specific ATM mutations in women under 40, we found no significant differences in pre-treatment characteristics or treatment related toxicity between patients with and without mutations.

In this retrospective correlation of cohort-specific mutations of the ATM gene, we observed a negative prognosis. Larger studies are needed to conclusively determine if specific ATM missense mutations predict a worse outcome in breast cancer.

Key Research Accomplishments

Construction of knock-in mice is in progress.

Reportable Outcomes

None in this first year.

Conclusion

Construction of the knock-in mice is in progress.

References

Singh A, Jung M, **Feng J**, Buzin C, Moulds J, Zhang Y, Gehan E, Dritschilo A, Sommer SS (2006): Clinical prognosis of breast cancer patients with ATM missense mutations. *Submitted*

Appendices

Steve S. Sommer, M.D., Ph.D. (CV)

CURRICULUM VITAE

Name: Steve S. Sommer, M.D., Ph.D.

Address: City of Hope National Medical Center
Beckman Research Institute
Departments of Molecular Genetics and Molecular Diagnosis
1500 East Duarte Road
Duarte, CA 91010-3000
Telephone: (626) 930-5497
Telefax: (626) 301-8142
E-mail: sommeradmin@coh.org

Education:

1968-1972	B.A., University of Pennsylvania, Philadelphia, PA
1972-1979	Cornell-Rockefeller, M.D., Ph.D. Fellowship
1978	Ph.D. - Rockefeller University, New York, NY (Molecular Biology)
1979	M.D. - Cornell University Medical College, New York, NY

Postdoctoral Training

Residencies and Clinical Fellowships

7/79-6/80	Resident, Surgical Pathology and Postmortem Section, Dr. Jose Costa, Chief; Laboratory of Pathology, Dr. Alan S. Rabson, Chief; National Cancer Institute, National Institutes of Health, Bethesda, MD
7/82-7/84	Multicenter Individual Fellowship in Clinical Genetics; sponsors, Dr. James Sidbury, Jr., Chief, Section on Developmental Biology and Human Nutrition, National Institute of Child Health and Human Development and Dr. Kenneth Rosenbaum, Director, Clinical Genetics, Children's Hospital National Medical Center, Washington, DC

Research Fellowships

7/80-7/85	Medical Staff Fellow, Section of the Genetics of Simple Eukaryotes, Dr. Reed Wickner, Chief; Laboratory of Biochemical Pharmacology, Dr. Herbert Tabor, Chief; National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD. Research area: molecular genetics of virus-like particles in yeast.

Academic Appointments:

7/85-6/90	Assistant Professor of Molecular Biology, Department of Biochemistry and Molecular Biology, Mayo Foundation School of Medicine, Rochester, MN; Mayo Clinic ranks: Senior Associate Consultant, 7/85-11/89; Consultant, 11/89-present.
7/90-6/94	Associate Professor of Molecular Biology, Department of Biochemistry and Molecular Biology, Mayo Foundation School of Medicine, Rochester, MN
7/94-8/96	Professor of Molecular Biology, Department of Biochemistry and Molecular Biology, Mayo Foundation School of Medicine, Rochester, MN
8/95-8/96	Director. Thrombosis and Haemostasis Molecular Diagnostic Laboratory, Division of Hematology, Mayo Foundation School of Medicine, Rochester, MN
8/96	Director, Department of Molecular Genetics, Beckman Research Institute, City of Hope, Duarte, CA
8/96	Director, Department of Molecular Diagnostics and Acting Chair, Division of Human Genetics, City of Hope National Medical Center, City of Hope, Duarte, CA

Licensure and Certifications:
Medical Licenses in Minnesota and California
American College of Medical Genetics
Diplomat in Clinical Genetics, 1984
Diplomat in Clinical Molecular Genetics, 1993 (97th percentile on certification exam)

Honors:
Cornell-Rockefeller Biomedical Fellowship, 1972-1979
Elected, American Society of Clinical Investigation (ASCI), 1992
Elected, Association of American Physicians (AAP), 1996

Editorships/Editorial Boards:
Editorial Board, PCR Methods and Applications, 1991-1993
Communicating Editor, Human Mutation, 1991-present
Editorial Board, BioTechniques, 1992-present
Editorial Board, Mutation Research Genomics, 1997-present

Patents

No. 5194600 (3/16/93): Genes, which participate in beta-glucan assembly and use thereof
No. 6207425 (3/27/01): Bidirectional PCR amplification of specific alleles
No. 6312905 (11/29/01): Method for detecting mutations in nucleic acids
No. 6376193 (4/23/02): Method for detecting mutations in nucleic acids
No. 6287441 (9/11/01): Multi Conditional SSCP ($SSCP_5$): A rapid method for mutation scanning with virtually 100% sensitivity.
No. 6534269B2 (3/18/03): Pyrophosphorolysis activated polylmerization (PAP): application to allele-specific amplification and nucleic acid sequence determination
No. 6582574 (6/24/03): PK-matched running buffers for gel electrophoresis.
No. 6,355,422 (3/12/02): Single tube PCR assay for detection of chromosomal mutations: application to the inversion hotspot in the factor VIII gene including optional use of subcycling PCR.
No. 6,027,913 (2/22/00): Nucleic acid amplification with direct sequencing.
No. 6,361,949(3/26/02): Nucleic acid amplification with direct sequencing.

Current and Past Extramural Support:

Source: U.S. Army BC990386
Title: **p53 Gene Mutagenesis in Breast Cancer** (Active) No Overlap
Dates: Total Project Period: 08/01/2000-02/01/2005

Major Goals: To compare patterns of p53 mutations occurring in the Midwest in the 1960's, to present day patterns.

Source: U.S. Army BC000761
Title: **Lipophilic Mutagens, Fat Consumption and Breast Cancer** (Active) No Overlap
Dates: Total Project Period: 03/31/2001-07/31/2005

Major Goals: To test the central hypothesis that mammary epithelial cells are susceptible to lipophilic mutagens concentrated in adjacent mammary adipocytes and originating in the diet.

Source: NIH-RO1 AG19784-01
Title: **Tissue-Specific Antioxidant Antimutagenesis** (Active) No Overlap
Dates: Total Project Period: 07/01/2001-06/30/2006

Major Goals: The Big Blue® Transgenic Mouse Mutation Detection System is utilized to examine the antimutagenic effect of lifetime administration of mega doses of antioxidants.

Source: National Hemophilia Foundation
Title: **Restoration of Factor VII/IX Function in Hemophilia A/B Patients** (Active) No Overlap
Dates: Total Project Period: 09/01/2001-08/31/2002

Major Goals: A pilot study to investigate aminoglycoside therapy in hemophilia

Source: NIH-1 R21 CA94408-01
Title: **Carbon Nanotubes: Artificial Gels for Mutation Detection** (Active) No Overlap
Total Project Period: 04/01/2002-07/01/2006

Major Goals: Artificial gels generated by carbon nanotubes will be utilized to miniaturize DOVAM-S, a mutation scanning method that detects virtually all mutations.

Source: NIH-1 R21 CA94334-01
Title: **PAP: A Platform Technology** (Active) No Overlap
Total Project Period: 07/01/2002-06/30/2006

Major Goals: Pyrophosphorolysis activated polymerization (PAP) offers a novel approach for retrieving multiple types of information from nucleic actids.

Source: NIA-1 R03 AG 20756-01
Title: **Aging and Mutation Load in Transgenic Medaka Fish** (Active) No Overlap
Total Project Period: 06/01/2002-05/31/2005

Major Goals: Medaka fish (*Oryzias latipes*) transgenic for the Big Blue mutation detection system are an excellent model for *in vivo* analysis of age and mutation load (mutation frequency and pattern) with consideration of associated parameters such as tissue type and certain environmental conditions, including temperature

Source: NIH-1 R01 HL70147-03
Title: **Translational Bypass in Patient with Hemophilia** (Active) No Overlap
Total Project Period: 09/15/2002-08/31/2005

Major Goals: We hypothesize that small molecules that readily enter cells can induce nonsense suppression by the protein synthetic apparatus such, that nonsense mutations are translationally bypassed at levels up to 20%. Evaluation of efficacy will be performed with the prototype drug gentamicin, an aminoglycoside antibiotic.

Source: DOD U.S. Army BC0440-16-01
Title: **Do Structural Missense Variants in the ATM Gene Found in Women with Breast Cancer Cause Breast Cancer in Knock-in Mouse Strains?**
Total Project Period: 12/01/04-11/30/2007 (Active) No Overlap

Major Goals: Test the hypothesis that the risk of breast cancer in ATM heterozygotes is due to a dominant negative effect of certain missense mutations in the gene by studying the effects in knock-in mouse models of ATM variants found in patients with breast cancer.

BIOGRAPHICAL SKETCH A: Methodology Development

Name	Position Title
Steve S. Sommer, M.D., Ph.D.	Professor of Molecular Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREES	YEAR(s)	FIELD OF STUDY
Rockefeller University, New York, NY	B.A.	1972-1978	Molecular Biology
Cornell University Med. College, New York, NY	Ph.D.	1972-1979	Medicine
NIH, Multicenter Indiv. Fellowship, Bethesda, Maryland	M.D.	1982-1984	Genetics
NIADDK, NIH, Medical Staff Fellow, Bethesda, Maryland		1980-1985	Genetics

Medical Specialties: ABMG Diplomate in Clinical Genetics (1984) and Clinical Molecular Genetics (1993)

Experience:

1980-1985:	*Medical Staff Fellow, Killer System of Yeast; with Dr. Reed Wickner, NIADDK, NIH*
1982-1984:	Multicenter Individual Fellowship in Clinical Genetics
7/85-8/96:	Assistant Associate and Full Professor of Molecular Biology, Department of Biochemistry and Molecular Biology, Mayo Foundation School of Medicine, Rochester, MN
8/96-Present:	Director, Departments of Molecular Genetics and Molecular Diagnosis, City of Hope, Duarte, CA

Selected papers emphasizing the development, validation, and extension of novel methods: 43 of 251 publications (206 published or in press original papers and 45 reviews, letters...)

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184. Liu, Q., and Sommer, S.S.: **Pyrophosphorolysis Activated Polymerization (PAP): Application to Allele-Specific Amplification.** BioTechniques 29: 1072-1083, 2000.
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BIOGRAPHICAL SKETCH B: Spontaneous Mutagenesis

Name	Position Title
Steve S. Sommer, M.D., Ph.D.	Professor of Molecular Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREES	YEAR(s)	FIELD OF STUDY
Rockefeller University, New York, NY	B.A.	1972-1978	Molecular Biology
Cornell University Med. College, New York, NY	Ph.D.	1972-1979	Medicine
NIH, Multicenter Indiv. Fellowship, Bethesda, Maryland	M.D.	1982-1984	Genetics
NIADDK, NIH, Med.Staff Fellow Bethesda, Maryland		1980-1985	Genetics

Medical Specialties: ABMG Diplomate in Clinical Genetics (1984) and Clinical Molecular Genetics (1993)

Experience:

1980-1985: Medical Staff Fellow, Killer System of Yeast; with Dr. Reed Wickner, NIADOX, NIH
1982-1984: Multicenter Individual Fellowship in Clinical Genetics
7/85-8/96: Assistant Associate and Full Professor of Molecular Biology, Department of Biochemistry and Molecular Biology, Mayo Foundation School of Medicine, Rochester, MN
8/96-Present: Director, Departments of Molecular Genetics and Molecular Diagnosis, City of Hope, Duarte, CA
8/96-Present: Medical Director, City of Hope Clinical Molecular Diagnostic Laboratory

Selected Papers: 23 of 251 publications (206 published or in press original papers and 45 reviews, letters...)

Human Germline Mutation: Lessons from the Factor IX gene

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BIOGRAPHICAL SKETCH C: Molecular Epidemiology

Name	Position Title
Steve S. Sommer, M.D., Ph.D.	Professor of Molecular Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREES	YEAR(s)	FIELD OF STUDY
Rockefeller University, New York, NY	B.A.	1972-1978	Molecular Biology
Cornell University Med. College, New York, NY	Ph.D.	1972-1979	Medicine
NIH, Multicenter Indiv. Fellowship, Bethesda, Maryland	M.D.	1982-1984	Genetics
NIADDK, NIH, Medical Staff Fellow, Bethesda, Maryland		1980-1985	Genetics

Medical Specialties: ABMG Diplomate in Clinical Genetics (1984) and Clinical Molecular Genetics (1993)

Experience:

1979-1980: Resident, Surgical Pathology and Postmortem Section; with Dr. Alan S. Rabson, National Cancer Institute, NIH
1980-1985: Medical Staff Fellow, Killer System of Yeast; with Dr. Reed Wickner, NIADOX, NIH
1982-1984: Multicenter Individual Fellowship in Clinical Genetics
7/85-8/96: Assistant Associate and Full Professor of Molecular Biology, Department of Biochemistry and Molecular Biology, Mayo Foundation School of Medicine, Rochester, MN
8/96-Present: Director, Departments of Molecular Genetics and Molecular Diagnosis, City of Hope, Duarte, CA
8/96-Present: Medical Director, City of Hope Clinical Molecular Diagnostic Laboratory

Selected papers emphasizing molecular epidemiology: 39 of 251 publications (206 published or in press original papers and 45 reviews, letters...)

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R36 Hartmann, A., Blaszyk, H., Kovach, J.S., and Sommer, S.S.: **The Molecular Epidemiology of P53 Gene Mutations in Human Breast Cancer.** Trends in Genetics 13:27-33, 1997.
191. Weinshenker, B.G., and Sommer, S.S.: **Vapse-Based Analysis: a two-phased candidate gene approach for elucidating genetic predisposition to complex disorders.** Mutation Research Genomics 458:7-17, 2001.

BIOGRAPHICAL SKETCH D: Clinical Testing

Name	Position Title
Steve S. Sommer, M.D., Ph.D.	Professor of Molecular Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREES	YEAR(s)	FIELD OF STUDY
Rockefeller University, New York, NY	B.A.	1972-1978	Molecular Biology
Cornell University Med. College, New York, NY	Ph.D.	1972-1979	Medicine
NIH, Multicenter Indiv. Fellowship, Bethesda, Maryland	M.D.	1982-1984	Genetics
NIADDK, NIH, Medical Staff Fellow, Bethesda, Maryland		1980-1985	Genetics

Medical Specialties: ABMG Diplomate in Clinical Genetics (1984) and Clinical Molecular Genetics (1993)

Experience:

1980-1985: Medical Staff Fellow, Killer System of Yeast; with Dr. Reed Wickner, NIADOX, NIH
1982-1984: Multicenter Individual Fellowship in Clinical Genetics
7/85-8/96: Assistant Associate and Full Professor of Molecular Biology, Department of Biochemistry and Molecular Biology, Mayo Foundation School of Medicine, Rochester, MN
8/96-Present: Director, Departments of Molecular Genetics and Molecular Diagnosis, City of Hope, Duarte, CA

Selected papers emphasizing the development, validation, and extension of novel methods: 31 of 251 publications (206 published or in press original papers and 45 reviews, letters...)

Clinical MolecularTesting

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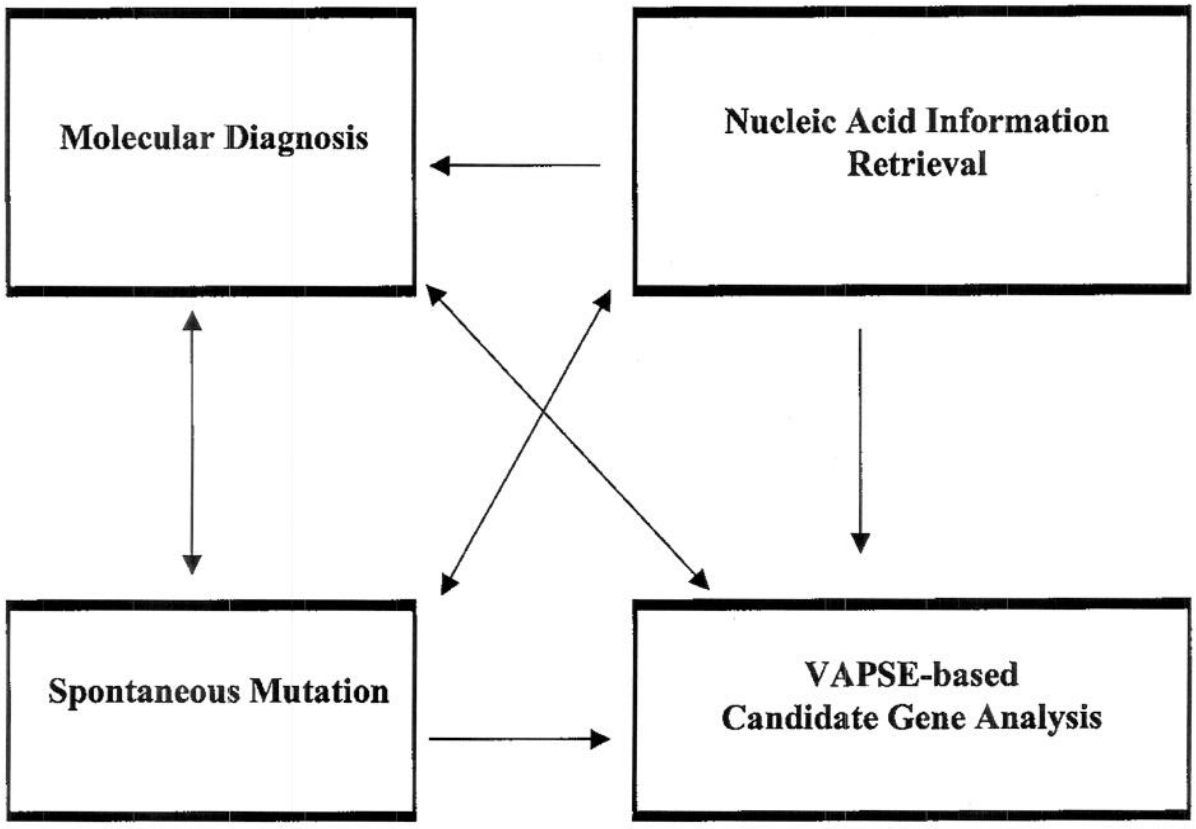
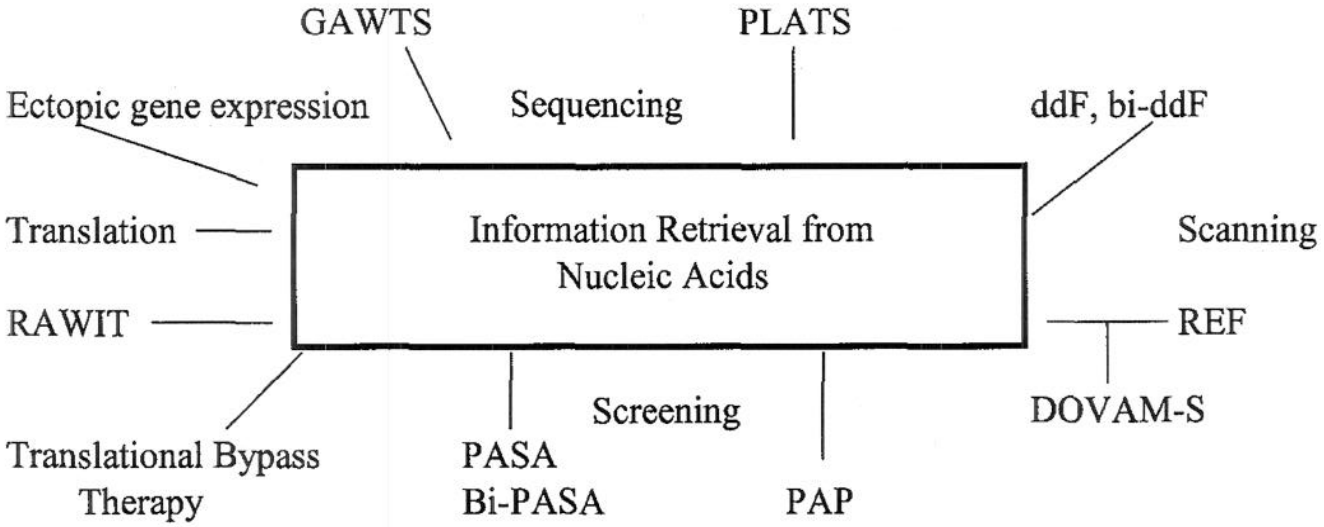
FOUR COMPONENTS OF THE LABORATORY

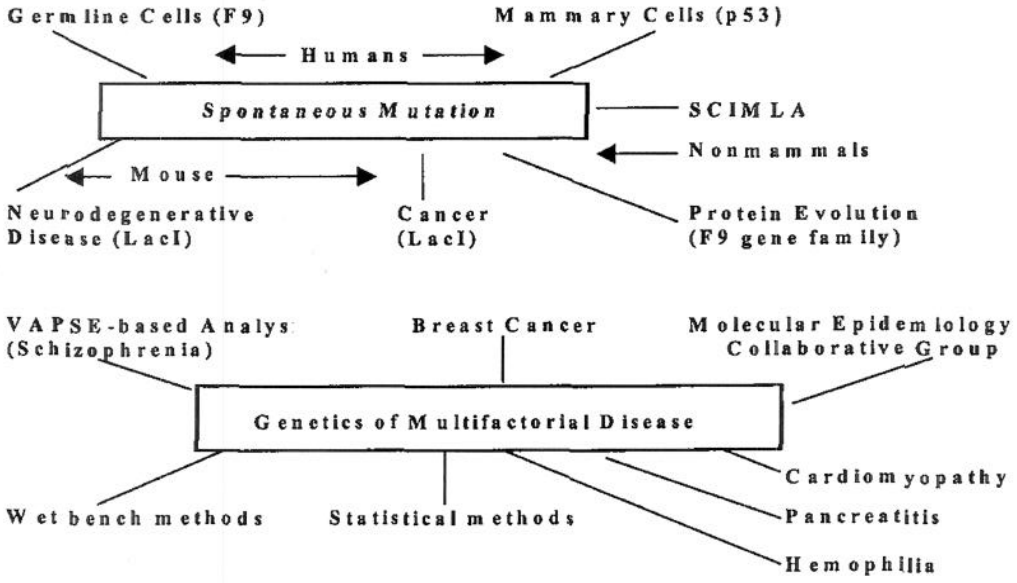


SCHEMATIC OF LABORATORY PROJECTS MADE POSSIBLE THROUGH INTERACTIONS WITH MANY EXCELLENT COLLABORATORS



Selected Additional Methods

PCR of high G+C templates; Restriction endonuclease fingerprinting; DNA stability in blood; UV inactivation of PCR contamination; Megapriming--duplex DNA of 200 bp can amplify human genomic DNA; PCR across great evolutionary distances; Protein truncation assays; Statistical methods for candidate gene association studies; pK-matched electrophoresis buffers



I. Original Publications, Peer Reviewed

1976 - 1980: mRNA Metabolism

1. Sommer, S.S., Salditt-Georgieff, M., Bachenheimer, S., Darnell, J.E., Furuichi, Y., Morgan, M., and Shatkin, A.J.: **The methylation of adenovirus-specific nuclear and cytoplasmic RNA.** Nucleic Acid Res. 3:749-765, 1976.
2. Sommer, S.S., Lavi, U., and Darnell, J.E.: **The absolute frequency of labeled m^6A in HeLa cell mRNA decreases with label time.** J. Mol. Biol. 124:487-499, 1978.
3. Sommer, S.S., and Rin, N.A.: **The lognormal distribution fits the decay profile of eukaryotic mRNA.** Biochem. Biophys. Res. Commun. 90:135-141, 1979.
4. Sommer, S.S.: **Prediction of the electrophoretic mobilities of nucleotides on neutral paper.** Anal. Biochem. 98:8-12, 1979.
5. Sommer, S.S., and Cohen, J.E.: **The size distributions of proteins, mRNA, and Nuclear RNA.** J. Mol. Evol. 15:37-57, 1980.

1982 - 1987: Yeast Molecular Genetics

6. Sommer, S.S., and Wickner, R.B.: **Co-curing of plasmids affecting killer double-stranded RNAs of Saccharomyces cerevisiae: [HOK], [NEX], and the abundance of L are related and further evidence that M_1 requires L.** J. Bacteriol. 150:545-551, 1982.
7. Sommer, S.S., and Wickner, R.B.: **Yeast L dsRNA consists of at least three distinct RNAs; evidence that the non-Mendelian genes [HOK], [NEX] and [EXL] are on one of these dsRNAs.** Cell 31:429-441, 1982.
8. Ridley, S.P., Sommer, S.S., and Wickner, R.B.: **Superkiller mutations in *Saccharomyces cerevisiae* suppress exclusion of M_2 Double-Stranded RNA by L-A-HN and confer cold sensitivity in the presence of M and L-A-HN.** Mol. Cell. Biol. 4:761-770. 1984.
9. Sommer, S.S., and Wickner, R.B.: **Double-Stranded RNAs that Encode Killer Toxins in *Saccharomyces cerevisiae*: Unstable size of M Double-Stranded RNA and Inhibition of M_2 Replication by M_{10}.** Mol. Cell. Biol. 4:1747-1753, 1984.
10. Icho, T., Lee, H.S., Sommer, S.S., and Wickner, R.B.: **Molecular characterization of chromosomal genes affecting double-stranded RNA replication in Saccharomyces cerevisiae.** Basic Life Sci. 40:165-171, 1986.
11. Sommer, S.S., and Wickner, R.B.: **Gene disruption indicates that the only essential function of the SKI8 chromosomal gene is to protect Saccharomyces cerevisiae from viral cytopathology.** Virology 157:252-256, 1987.

1986: Human Molecular Genetics

12. Sommer, S.S.: ***Need for guidelines for reporting of recombination* between a gene and a closely linked polymorphism.** Lancet i:1101, 1986.

1987: Information Retrieval from Nucleic Acids

13. Gustafson, S., Proper, J.A., Bowie, E.J.W., and Sommer, S.S.: **Parameters affecting the yield of DNA from human *blood*.** Anal. Biochem.165:294-299, 1987.
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1988: Information Retrieval from Nucleic Acids

15. Stoflet, E.S., Koeberl, D.D., Sarkar, G. and Sommer, S.S.: **Genomic amplification with transcript sequencing.** Science 239:491-494, 1988.
16. Sarkar, G., and Sommer, S.S.: **RNA amplification with transcript sequencing (RAWTS).** Nucleic Acids Res. 16:5197, 1988.
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1989: Pattern of Spontaneous Mutation

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1989: Information Retrieval from Nucleic Acids

22. Schowalter, D.B., and Sommer, S.S.: **The generation of radiolabeled DNA and RNA probes with polymerase chain reaction.** Anal. Biochem. 177:90-94, 1989
23. Sarkar, G., and Sommer, S.S.: **Access to a messenger RNA sequence or its protein product is not limited by tissue or species specificity.** Science 244:331-334, 1989.
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1990: Yeast Molecular Genetics

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1990: Pattern of Spontaneous Mutation

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1990: *Information* Retrieval from Nucleic Acids

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1991: Pattern of Spontaneous Mutation

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49. Bottema, C.D.K., Ketterling, R.P., Ii, S., Yoon, H-S., Phillips, J.A.,III, and Sommer, S.S.: **Missense mutations and evolutionary conservation of amino acids: evidence that many of the amino acids in factor IX function as "spacer" elements.** Am. J. Hum. Genet. 49:820-838, 1991.
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1991: Information Retrieval and Analysis from Nucleic Acids

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Methodology Described Within Other Papers

56. *Computer software for estimating steady state dinucleotide compositions of genomic DNA given 96 possible* dinucleotide mutation rates and, conversely, estimating a minimal set of 96 dinucleotide mutation rates given a set of *genomic dinucleotide frequencies* (Bottema et al., 1991: reference 50).

1991: Genetic Predisposition to Schizophrenia

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1992: Pattern of Spontaneous Mutation

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59. Sommer, S.S., Bowie, E.J.W., Ketterling, R.P., and Bottema, C.D.K.: **Missense mutations and the magnitude of functional deficit: the example of factor IX.** Hum. Genet. 89:295-297, 1992.
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1992: Information Retrieval and Analysis from Nucleic Acids

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1992: Genetic Predisposition to Schizophrenia

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1993: Yeast Molecular Genetics

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1993: Spontaneous Mutation

69. Ketterling, R.P., Vielhaber, E., Bottema, C.D.K., Schaid, D.J., Cohen, M.P., Sexauer, C.L., and Sommer, S.S.: **Germline origins of mutation in families with hemophilia B: the sex ratio varies with the type of mutation.** Am. J. Hum. Genet. 52:152-166, 1993.

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1993: Information Retrieval and Analysis from Nucleic Acids

Dutton, C.M., Paynton, C., and Sommer, S.S.: **General method for amplifying regions of very high G + C content.** Nucleic Acids Res. 21(12):2953-2954, 1993.
81. Schaid, D.J., and Sommer, S.S.: **Genotype relative risks: methods for design and analysis of candidate-gene association studies.** Am. J. Hum. Genet. 53:1114-1126, 1993.

Methodology Described In Other Papers

Statistical methodology and computer software for obtaining unbiased sex ratios of mutation from molecular data given the pedigree structure of the ascertained families (see Ketterling et al., Reference 68).
Statistical approach for addressing the problem of multiple comparisons in candidate gene analyses of multifactorial disease (see Sobell et al., reference 81).

1993: Genetic Predisposition to Schizophrenia

Sobell, J.L., Heston, L.L., and Sommer, S.S.: **Novel association approach for determining the genetic predisposition to schizophrenia: case-control resource and testing of the first candidate gene.** Am. J. Med. Genet. (Neuropsychiatric Genetics) 48:28-35, 1993.
84. Sommer, S.S., Lind, T.J., Heston, L.L., and Sobell, J.L.: **Dopamine D_4 receptor variants in unrelated schizophrenic cases and controls.** Am. J. Med. Genet. (Neuropsychiatric Genetics) 48:90-93, 1993.
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86. Arnholt, J.C., Sobell, J.L., Heston, L.L., and Sommer, S.S.: **APP mutations and schizophrenia.** Biol. Psychiatry 34:739-740, 1993.
87. Lindor, N.M., Sobell, J., Heston, L., Thibodeau, S.N., and Sommer, S.S.: **Screening the dystrophin gene suggests a high rate of polymorphism in general but no exonic deletions in schizophrenics.** Am. J. Med. Genet. (Neuropsychiatric Genetics) 54:1-4, 1994.

1994: Spontaneous Mutation

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96. Blaszyk, H., Vaughn, C.B., Hartmann, A., McGovern, R.M., Schroeder, J.J., Cunningham, J., Schaid, D., Sommer, S.S., and Kovach, J.S.: **Novel pattern of p53 gene mutations in an American black cohort with high mortality from breast cancer.** Lancet 343:1195-1197, 1994.
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99. Knöll, A., Jacobson, D.P., Kretz, P.L., Lundberg, K.S., Short, J.M., and Sommer, S.S.: **Spontaneous mutations in *lacI*-containing λ lysogens derived from transgenic mice: the observed patterns differ in liver and spleen.** Mutation Research 311:57-67, 1994.

1994: Information Retrieval and Analysis from Nucleic Acids

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